

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28860 A2

(51) International Patent Classification⁷: **C07D 487/04**,
A61K 31/4985, 31/519, 31/437, 31/4365, A61P 29/00,
37/00, C07D 471/04, 513/04 // (C07D 487/04, 241:00,
235:00) (C07D 487/04, 239:00, 231:00) (C07D 471/04,
235:00, 221:00) (C07D 513/04, 277:00, 221:00)

[CN/US]; 1189 Washington Street, D22, Middletown, CT
06457 (US). **ZUSI, Fred, C.** [US/US]; 20 Nolan Road,
Hamden, CT 06514 (US).

(21) International Application Number: PCT/US01/42387

(74) Agents: **WINSLOW, Anastasia** et al.; Bristol-Myers
Squibb Company, P.O. Box 4000, Princeton, NJ
08543-4000 (US).

(22) International Filing Date:
27 September 2001 (27.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.

(30) Priority Data:
60/223,304 3 October 2000 (03.10.2000) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

(71) Applicant (*for all designated States except US*): **BRIS-
TOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box
4000, Route 206 and Provinceline Road, Princeton, NJ
08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BEAULIEU, Fran-
cis** [CA/CA]; 370 Leotable Dubuc, Laprairie, Québec
J5R 5M4 (CA). **OUELLET, Carl** [CA/CA]; 555 De
La Verendrye, Boucherville, Québec J4B 2Y3 (CA).
BELEMA, Makonen [ET/US]; 345 Willow Street, New
Haven, CT 06511 (US). **QIU, Yuping** [CN/US]; 397 Con-
estoga Street, Windsor, CT 06095 (US). **YANG, Xuejie**

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: AMINO-SUBSTITUTED TETRACYCLIC COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS AND
PHARMACEUTICAL COMPOSITIONS COMPRISING SAME

(57) Abstract: Compounds of formula (I), or pharmaceutically-acceptable salts thereof, are useful in treating inflammatory and
immune diseases and disorders, wherein X₁ Y₁ Y₂ and R₂-R₄ are as defined in the specification.

WO 02/28860 A2

AMINO-SUBSTITUTED TETRACYCLIC COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS AND PHARMACEUTICAL COMPOSITIONS COMPRISING SAME

5

Background of the Invention

Tumor necrosis factor (TNF- α) is a potent cytokine having pro-inflammatory properties that is released by many cell types when stimulated. Studies have shown a relationship between elevated levels of TNF- α and a
10 variety of diseases including septic shock, hematopoiesis, tumors, inflammatory disorders of the central nervous system including HIV encephalitis, cerebral malaria, and meningitis, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Creutzfeldt-Jacob disease.

Recently, attention has focussed on the role of Nuclear factor- κ B (NF- κ B)
15 in the activation pathway that leads to production of TNF- α and other inflammatory cytokines and gene types. Besides TNF- α , NF- κ B modulates many genes involved in immune function and inflammation, including IL-2, IL-6, IL-8, IL-2R α , GM-CSF, intercellular adhesion molecule (ICAM-1), and vascular cellular adhesion molecule-1 (VCAM-1). Thus, inhibition of NF- κ B and/or its activation
20 pathway provides a means for treating a wide range of diseases.

Potential inhibitors of NF- κ B and/or the NF- κ B pathway have been identified as including Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants. I κ B is a cytoplasmic protein that controls NF- κ B activity by retaining NF- κ B in the cytoplasm. I κ B is phosphorylated by the I κ B
25 kinase (IKK), which has two isoforms, IKK- α (or "IKK-1") and IKK- β (or IKK-2). Upon phosphorylation of I κ B by IKK, NF- κ B is rapidly released into the cell and translocates to the nucleus where it binds to the promoters of many genes and up-regulates the transcription of pro-inflammatory genes. Glucocorticoids

reportedly inhibit NF- κ B activity by two mechanisms, *i.e.*, upregulating I κ B protein levels and inhibiting NF- κ B subunits. Nitric oxide also reportedly inhibits NF- κ B through upregulation of I κ B. However, these mechanisms of interaction are complex; for example, production of nitric oxide in lymphocytes reportedly
5 enhances NF- κ B activity.

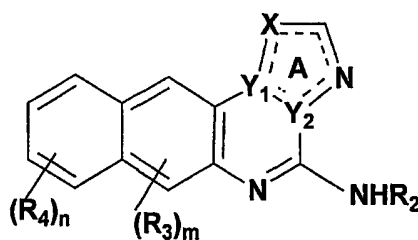
As may be appreciated, those in the field of pharmaceutical research continue to seek to develop new compounds and compositions having increased effectiveness, bioavailability, and solubility, having fewer side effects, and/or providing the consumer with a choice of options. The present invention provides
10 4-amino substituted benzoquinoline, benzoquinoxaline, and benzoquinazoline compounds having five-membered heterocycles (*e.g.*, pyrazolyl, imidazolyl, and thiazolyl rings) fused thereto that are useful as anti-inflammatory agents and/or for treating conditions associated with TNF- α and NF- κ B.

Lactam-based tetracyclic compounds useful as antagonists of NMDA (*N*-methyl-D-aspartate) and AMPA (α -3-hydroxy-5-methylisoxazole-4-propionate) receptors are disclosed in WO 94/07893 and Mignani, Aloup, *et al.*, Drug. Dev. Res., Vol. 48 (3) (1999), at pp. 121-29, and Heterocycles, Vol. 50, No. 1 (1999), at pp. 259-267. Compounds such as lactams claimed to be useful for blocking excitatory amino acid receptors are shown in U.S. Pat. Nos. 5,153,196 and
15 5,196,421. Tricyclic compounds having amino-substituents are disclosed in U.S. Pat. No. 5,182,386, assigned to Neurogen Corp., and in US Patents Nos. 4,160,097, 4,172,947, 4,191,766, 4,191,767, 4,198,508, 4,200,750, 4,225,724, and 4,236,015, in WO97/19,079, and in S. Ceccarelli *et al.*, European Journal of Medicinal Chemistry Vol. 33, (1998), at pp. 943-955. To applicants' knowledge,
20 4-amino substituted tetracyclic compounds according to formula (I) have not

been previously described. The patents and articles cited above are incorporated herein by reference.

Summary of the Invention

5 The invention is directed to a compound of the formula (I), useful in treating inflammatory or immune diseases or disorders:



(I),

or a pharmaceutically-acceptable salt thereof, wherein

X is NR₁, CR₁, or S;

15 Y₁ and Y₂ are nitrogen or carbon, provided that

a) when X is CR₁, at least one of Y₁ and Y₂ is nitrogen, and b) when one of Y₁ and Y₂ is carbon, the other of Y₁ and Y₂ is nitrogen and/or X is NR₁ or S, so that ring A defines a five-membered heteroaryl ring having at least two heteroatoms;

20 R₁ is hydrogen, halogen, alkyl, substituted alkyl, cyano, OR₅, NR₅R₆, C(=O)R₅, CO₂R₅, or aryl;

R₂ is alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclo, cycloalkyl, or substituted cycloalkyl;

25 R₃ and R₄ are independently selected from halogen, alkyl, substituted alkyl, nitro, cyano, OR₇, NR₇R₈, C(=O)R₇, CO₂R₇, C(=O)NR₇R₈, NR₇C(=O)R₈, NR₇C(=O)OR₈, S(O)_qR₇, NR₇SO₂R₈, and SO₂NR₇R₈;

R₅, R₆, R₇, and R₈ are independently selected from hydrogen, alkyl, substituted alkyl, and phenyl, or when attached to the same nitrogen atom (as in NR₅R₆ or NR₇R₈) may join together to form a heterocycle or heteroaryl;

m, *n* and *q* are independently 0, 1, or 2.

5

Advantageously, R₂ is an alkyl optionally substituted with OR' or NR'R", as defined in the specification. The invention also relates to pharmaceutical compositions containing at least one compound of formula (I) and a pharmaceutically-acceptable carrier or diluent. Also included within the invention is the use of compounds according to formula (I) for treating inflammatory and immune diseases.

10

Detailed Description of the Invention

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

15

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred. When numbers appear in subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, "C₁₋₆alkyl" refers to straight and branched chain alkyl groups with one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, and so forth.

20

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, or three substituents selected from the group consisting of halo, amino, cyano, hydroxy, alkoxy, alkylthio, -C(=O)H, -CO₂H, -(C=O)alkyl, -CO₂alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, or heterocycle. Thus,

25

the term "substituted alkyl" includes a polyfluoroalkyl, *i.e.*, where two or more hydrogen atoms of an alkyl chain are replaced by a fluorine atom, such as with trifluoromethyl. The term "substituted alkyl" also includes an alkyl group as defined above having the substituent NR'R", wherein each of R' and R" are
5 independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, -C(=O)H, -CO₂H -(C=O)alkyl, -CO₂-alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocycle. Alternatively, R' and R" may together form a heterocycle or heteroaryl ring. A substituted lower alkyl or substituted C₁₋₄alkyl refers to an alkyl group of 1-4 carbon atoms having one to
10 three substituents selected from those recited above for alkyl groups generally.

The term "alkoxy" refers to an alkyl group as defined above bonded through an oxygen atom (-O-), and the term "alkylthio" refers to an alkyl group as defined above bonded through a sulfur atom (-S-). For example, such groups include methoxy, methylthio, ethoxy, ethylthio, n-propoxy, n-propylthio,
15 isopropoxy, isopropylthio, n-butoxy, n-butylthio, tert-butoxy, tert-butylthio, n-pentoxy, n-pentylthio, and so forth.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups having 2 to 6 carbon atoms and one double bond are most preferred.
20 Exemplary alkenyl groups include ethenyl, 1-methyl-ethenyl, 1- or 2-propenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 1,1-dimethyl-2-propenyl, 2-methyl-2-propenyl, 1- , 2- or 3-butenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 3,3-dimethyl-1-butenyl, 2,3-dimethyl-1-butenyl, 1-methyl-2-butenyl, 1,1-dimethyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1,3-butadienyl, 1,3-
25 dimethyl-1,3-butadienyl, 1-, 2-, 3- or 4-pentenyl, and so forth.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred. Exemplary

alkynyl groups include ethynyl, 1- or 2-propynyl, 1-methyl-2-propynyl, 1,1-dimethyl-2-propynyl, 1-, 2- or 3-butynyl, 3-methyl-1-butynyl, 3,3-dimethyl-1-butynyl, 1-methyl-2-butynyl, 1,1-dimethyl-2-butynyl, 1-, 2- 3, or 4-pentynyl, and so forth.

- 5 The term "amino" when used alone refers to NH_2 . When used to define a substituent, as in 4-amino substituted tetracycles, the term "amino" refers to the group $\text{NR}'\text{R}''$, wherein R' and R'' are as defined above for alkyl.

 The term "carbonyl" refers to $-\text{C}(=\text{O})-$, and "carboxy" refers to $-\text{CO}_2-$. Thus, carbonyl C_{1-4} alkyl refers to the group $-\text{C}(=\text{O})$ linked to a C_{1-4} alkyl.

- 10 The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

 The term "cycloalkyl" refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7, carbon atoms as well as such rings having a fused aryl ring such as indan or a bridge of three to four carbon atoms as in bicycloheptane.

- 15 The term "substituted cycloalkyl" refers to such rings having one, two, or three substituents, preferably one, selected from the group consisting of alkyl, substituted alkyl, alkoxy, alkylthio, halo, hydroxy, cyano, amino, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2$ lower alkyl, aryl, heterocyclo, heteroaryl, keto ($=\text{O}$), $=\text{N}-\text{OH}$, $=\text{N}-\text{O}$ -lower alkyl, and a five or six membered ketal, *i.e.*, 1,3-dioxolane or 1,3-dioxane.
- 20

- The term "aryl" refers to phenyl, 1-naphthyl and 2-naphthyl, with phenyl being preferred. When the term "aryl" is used, it encompasses such rings having from zero, one, two or three substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, alkylthio, halo, hydroxy, nitro, cyano, amino, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{CO}_2\text{H}$, $-(\text{C}=\text{O})\text{alkyl}$, $-\text{CO}_2$ -alkyl, cycloalkyl, substituted cycloalkyl, $-(\text{C}=\text{O})\text{NH}_2$, $-(\text{C}=\text{O})\text{NH}(\text{alkyl})$, $-(\text{C}=\text{O})\text{NH}(\text{cycloalkyl})$, -
- 25

(C=O)N(alkyl)₂, -NH-CH₂-CO₂H, -NH-CH₂-CO₂-alkyl, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, heterocyclo, and heteroaryl.

The term "heterocyclo" or "heterocycle" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. When the heterocyclo is monocyclic, five- or six-membered rings are preferred; when bicyclic, fused 5,6- or 6,6-membered ring systems are preferred; and when tricyclic, ring systems having one five and two six membered rings, or three six membered rings, are preferred. Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom.

Whenever the term "heterocyclo" or "heterocycle" is used, any ring of the heterocyclo group may optionally contain one, two, or three substituents selected from the group consisting of halo, amino, cyano, alkyl, substituted alkyl, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, -CO₂H, -CO₂-alkyl, cycloalkyl, substituted cycloalkyl, -(C=O)NH₂, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)₂, -NH-CH₂-CO₂H, -NH-CH₂-CO₂-alkyl, heterocyclo, heteroaryl, keto, =N-OH, =N-O-lower alkyl, and a five or six membered ketal, *i.e.*, 1,3-dioxolane or 1,3-dioxane.

Exemplary monocyclic groups include tetrahydrothienyl, tetrahydrofuryl, azetidiny, pyrrolidiny, oxetany, imidazoliny, oxazolidiny, isoxazoliny, thiazolidiny, isothiazolidiny, tetrahydrofurany, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolodiny, 2-oxoazepiny, azepiny, 4-piperidony, tetrahydropyrany, morpholiny, thiamorpholiny, thiamorpholiny sulfoxide, thiamorpholiny sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothiényl and the like. Exemplary bicyclic heterocyclo groups include quinuclidiny.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. When the heteroaryl is monocyclic, five- or six membered rings are preferred; when bicyclic, fused 5,6- or 6,6-membered ring systems are preferred; and when tricyclic, ring systems having one five and two six membered rings, or three six-membered rings, are preferred. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring.


Whenever the term "heteroaryl" is used herein, any ring of the heteroaryl group may optionally contain one, two or three substituents selected from the group consisting of halo, amino, cyano, alkyl, substituted alkyl, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl,


phenylethyl, phenyloxy, phenylthio, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{-alkyl}$, cycloalkyl, substituted cycloalkyl, $-(\text{C}=\text{O})\text{NH}_2$, $-(\text{C}=\text{O})\text{NH(alkyl)}$, $-(\text{C}=\text{O})\text{NH(cycloalkyl)}$, $-(\text{C}=\text{O})\text{N(alkyl)}_2$, $-\text{NH-CH}_2\text{-CO}_2\text{H}$, $-\text{NH-CH}_2\text{-CO}_2\text{-alkyl}$, heterocyclo, and heteroaryl.

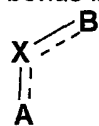
Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl,
 5 pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, and the like.

Exemplary bicyclic heteroaryl groups include indolyl, isoindolyl,
 benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl,
 10 tetrahydroisoquinolyl, isoquinolyl, benzimidazolyl, benzopyranyl, indolizyl, benzofuranyl, isobenzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolyl, quinoxalyl, quinazolyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolyl, naphthyridinyl, pteridinyl, and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl,
 15 phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

When reference is made herein to a bond having a solid and dashed line, such as in [], it should be understood that the bond(s) may be selected from a single or a double bond, as appropriate, given selections for adjacent

atoms. For example, when there is shown  , if X is sulfur or NH, the
 20 bonds linking X to adjacent atoms A and B are single bonds. However, when in



X is CR_1 or a nitrogen atom, one of the bonds linking X to A or B is a double bond and the other is a single bond.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

The compounds of formula I form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases.

5 In addition, the term "salt(s)" may include zwitterions (inner salts), *e.g.*, when a compound of formula I contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the
10 cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of the formula I with an amount of
15 acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates,
20 borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates,
25 lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric

acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as TEA, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-phenamine, N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others. Sodium or potassium salts are preferred.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, and/or a salt and/or solvate thereof. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula I-II compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C₁₋₆alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆

alkanoyloxy-C₁₋₆alkyl, e.g. acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C₁₋₆alkoxycarbonyloxy-C₁₋₆alkyl, e.g. methoxycarbonyloxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Compounds of the formula I and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have *trans* and *cis* (E and Z) isomers and may contain one or more chiral centers, therefore existing in enantiomeric and diastereomeric forms. The invention includes all such isomers, as well as mixtures of *cis* and *trans* isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers). When no specific mention is made of the configuration (*cis*, *trans* or R or S) of a compound (or of an asymmetric carbon), then any one of the isomers or a mixture of more than one isomer is intended.

Methods of Preparation

The inventive compounds may be prepared by methods such as those illustrated in the following Schemes I to V. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art. For all of the schemes and compounds, the groups R₁, R₂, R₃ and R₄ are as described herein for a compound of formula I, unless otherwise indicated. Groups designated R', as well as solvents, temperatures, pressures, and other reaction conditions, may be selected by one of ordinary skill in the art. For example, in these schemes chlorinating agents may include phosphorous oxychloride, catalytic agents may include metals such as Pd, and solvents may be selected

from 1,2-dichlorobenzene, methylene chloride, DMF, THF, alcohols, ethers, dioxane, acetonitrile, water, mixtures of ethers and water, and the like.

Abbreviations

5 For ease of reference the following abbreviations are used in the schemes and Examples herein:

Me = methyl
Et = ethyl
10 MeOH = methanol
EtOH = ethanol
i-PrOH = isopropanol
Ph = phenyl
Bz = benzyl
15 DCM = dichloromethane
DMF = dimethyl formamide
DMSO = dimethyl sulfoxide
NaOH = sodium hydroxide
TEA or Et₃N = triethylamine
20 TFA = trifluoroacetic acid
THF = tetrahydrofuran
K₂CO₃ = potassium carbonate
Na₂S₂O₃ = sodium thiosulfate
min = minute(s)
25 L = liter
mL = milliliter
μL = microliter
g = gram(s)
mg = milligram(s)
30 mol = moles
mmol = millimole(s)
meq = milliequivalent
RT = room temperature
sat or sat'd = saturated
35 aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS = mass spectrometry
40 NMR = nuclear magnetic resonance
mp = melting point

Definitions of Terms Used in the Reaction Schemes

The following are definitions of terms used herein and in the reaction schemes.

"Acetal, ketal, thioacetal or thioketal formation" are processes known in the art and illustrated in "Protective Groups in Organic Synthesis", Second Ed., T. W. Green and P. G. W. Wuts, John Wiley & Sons, New York, 1991, Chapter 4 and references therein, incorporated herein by reference.

"Acid halide formation" includes methods of converting a carboxylic acid to an acid halide. For example, this reaction may be performed with thionyl chloride, oxalyl chloride or bromide in the presence of DMF in DCM and phosphorus trichloride or tribromide.

"Alkylation" includes all alkylation procedures such as alkylation of desired alcohol or ketone groups by treatment with organic or inorganic base in an appropriate organic solvent, followed by addition of an alkylating agent such as an alkyl, allyl or benzyl halide, mesylate or tosylate to the generated enolate, phenolate or thiophenolate.

"Aromatic substitution" includes all aromatic substitution methods known in the field including nucleophilic substitutions of aromatic halides by water in presence of sulfuric acid or trifluoroacetic acid, or by alkoxides, aryloxides, thioalkoxides or thioaryloxides in an inert organic solvent. Copper salts may be used to promote the reaction of aryl halides with alkoxides, and Pd(0) salts may be used to promote the reaction with thioalkoxides.

"Aromatic halogenation" includes the addition of chlorine, bromine or iodine to an aromatic ring optionally with a catalyst, e.g. iron or a Lewis acid. It also includes the reaction of N-chloro and N-bromoamides catalyzed by the addition of acids. For iodination, iodine may be used with copper salts, silver trifluoromethanesulfonate, thallium(I) acetate, or with an oxidizing agent such as

nitric acid, iodic acid, sulfur trioxide or hydrogen peroxide. Iodine monochloride can also be used.

"Cross-coupling" includes all cross-coupling methods known by those skilled in the art. Such methods include the reaction of a vinyl or aromatic triflate, bromide or iodide with a tin (Stille-type), zinc, magnesium or boronate (Suzuki-type) derivative catalyzed by a palladium(0), palladium(II), nickel(0) or nickel(II) catalyst. Copper iodide, lithium chloride, zinc chloride or triphenylarsine, tris(2-furyl)phosphine or tris(2,4,6-trimethoxyphenyl)phosphine advantageously may also be added. When a boronic acid derivative is used, the reaction proceeds in the presence of an inorganic base such as potassium phosphate or carbonate or sodium carbonate. The cross-coupling reactions are performed in an inert organic solvent.

"Grignard type reaction" includes the addition of an organometallic compound to a carbonyl-containing compound. This includes addition of Grignard reagents, alkyl or aryllithiums, alkylzinc, alkylaluminum, organotitanium, organozirconium or organocerium compounds in an inert organic solvent such as ethyl ether, THF, DCM, benzene, toluene, or the like. Complexing of the ketone or the Grignard reagent with cerium halides, perchlorate salts or tetraalkylammonium halides may sometimes be advantageous to improve the addition reaction. The term "Grignard type reaction" is also intended to include the addition of a Grignard reagent to an acid chloride that has been first reacted with tributylphosphine to form the corresponding phosphonium salt. The reaction is performed in an inert organic solvent.

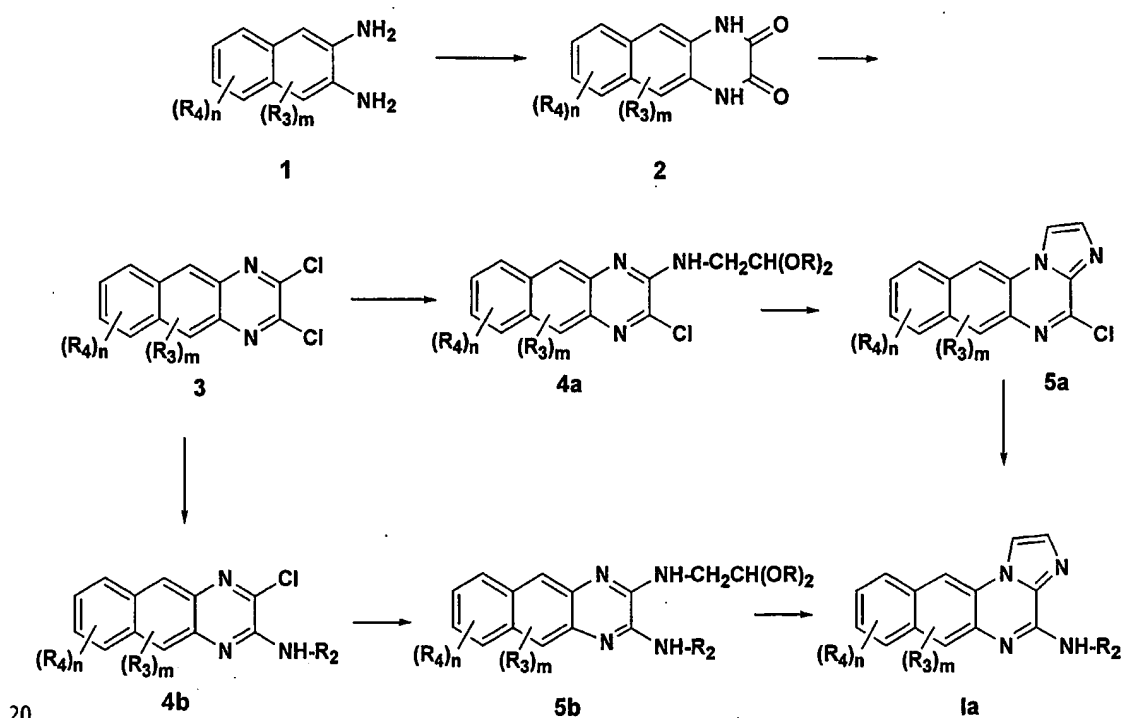
"Hydrolysis" includes the hydrolysis of esters and carbonyl protecting groups. For example, methyl or ethyl esters may be removed with aqueous solutions of sodium or potassium alkoxides in THF or EtOH. The hydrolysis of tert-butyl esters advantageously is carried out under acidic conditions such as 90% trifluoroacetic acid or 6N hydrochloric acid in solvents such as THF or DCM.

Allyl esters may be removed with Pd(0) catalyst in an organic solvent. Silyl esters such as trimethylsilylethyl esters may be cleaved with tetrabutylammonium fluoride in THF. The hydrolysis of ketals and acetals may be carried out under acidic conditions such as 1N hydrochloric acid, 80% acetic acid or p-toluenesulfonic acid in solvents such as THF or acetone.

"Imine formation" procedures are known in the field. For example, a ketone may be reacted with an amine in presence of an acid with or without a drying agent. Various inorganic and organic acids may be used, such as zinc chloride, titanium chloride, hydrochloric acid, sulfuric acid, trifluoroacetic acid, acetic acid, p-toluenesulfonic acid and the like, in solvents such as DCM, EtOH, benzene, toluene, THF, DMF and the like.

Scheme I
Benzo-imidazo-quinoxalines

15



20

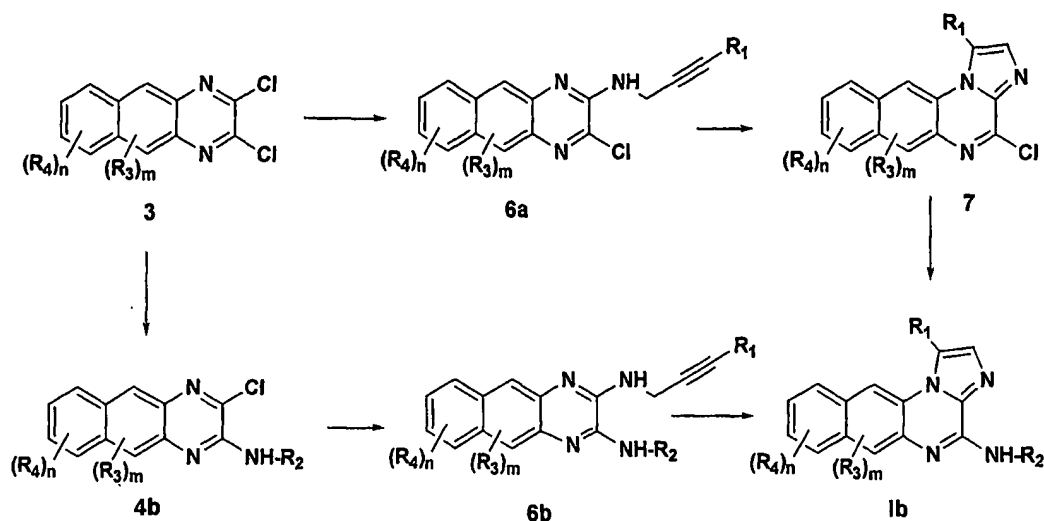
Benzo-imidazo-quinoxalines of formula 1a (wherein Y_1 of formula I is N, X is CR_1 and R_1 is hydrogen) may be prepared as above. Substituted 2,3-diaminonaphthalenes 1 are reacted with, for example, diethyl oxalate or oxalyl chloride to give annulated quinoxalinediones 2. Diones 2 are reacted with a chlorinating agent to give dichlorides 3. Dichlorides 3 are reacted with amine reagents comprising aminoacetaldehyde acetal and an appropriate primary amine (R_2-NH_2), and cyclized, wherein the order of reactivity may be adjusted depending upon chlorine atom reactivity.

For example, dichlorides 3 may first be reacted with an aminoacetaldehyde acetal to give amino-chloro derivatives 4a. The amino-chloro derivatives 4a may be cyclized to give the chloro-benzo-imidazoquinoxaline 5a, which may, in turn, be reacted with various primary amines (R_2-NH_2) to give compounds of formula (1a).

Alternatively, where the undesired chlorine atom has greater reactivity (e.g., due to substituents R_3 and R_4), the order of addition of the amine reagents can be reversed, as shown for structures 4b and 5b. Dichloride 3 is reacted with primary amines (R_2-NH_2) to give amino-chloro derivatives 4b, which are then reacted with an aminoacetaldehyde acetal to give diamino compounds 5b, which are then cyclized to give the compound of formula 1a.

Exemplary aminoacetaldehyde acetals comprise amino-acetaldehyde, dimethyl acetal, or aminoacetaldehyde, diethyl acetal. Cyclization is typically performed under acidic conditions.

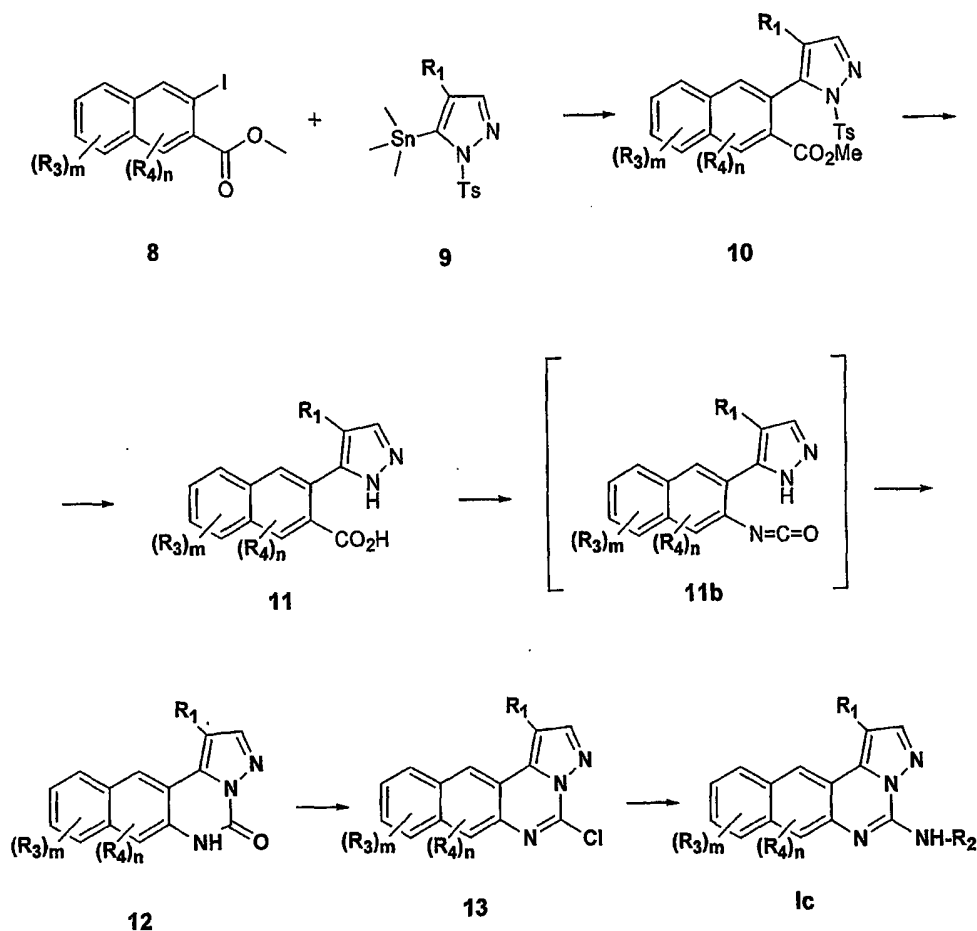
Scheme II
1-Substituted benzo-imidazo-quinoxalines



1-Substituted benzo-imidazo(1,2-a)quinoxalines of formula Ib (wherein Y_1 of formula I is N, X is CR_1 and R_1 is substituted lower alkyl) may be prepared as shown in Scheme II. Dichloro compounds 3 are prepared as shown in Scheme I and reacted with substituted propargylamines ($R_1-C\equiv C-CH_2-NH_2$) to give amino-chloro derivatives 6a, which are cyclized to 1-substituted chloro-benzo-imidazoquinoxalines 7. Suitable primary amines are reacted with 7 to give compounds of formula Ib.

Alternatively, the order of reactivity may be adjusted, wherein dichloro compounds 3 are first reacted with suitable primary amines to give derivatives 4b, as in Scheme I, and then reacted with propargyl amines to amino derivatives 6b, which may be cyclized as above to give compounds of formula Ib.

Scheme III

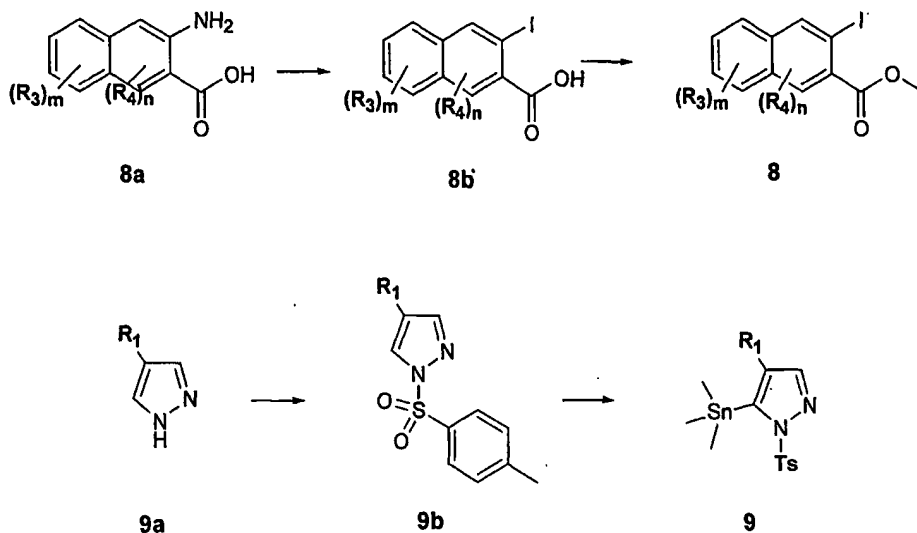
Benzo-pyrazolo-quinazolines

5

Benzo-pyrazolo-quinazolines of formula 1c (wherein Y_2 of formula I is N, X is CHR_1 and R_1 is as defined above) may be prepared as shown in Scheme III.

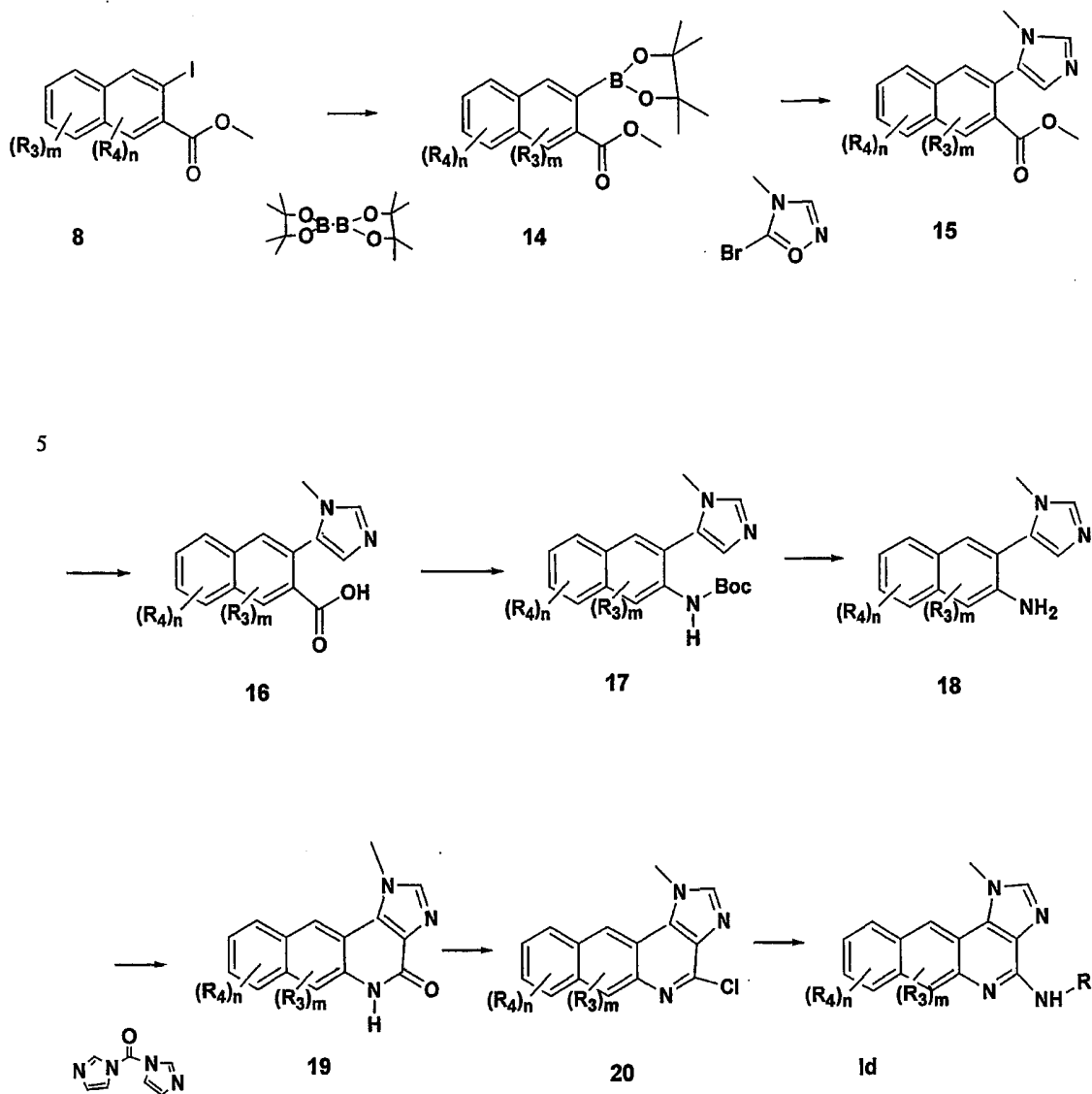
10 Reagents 8c and 9c are condensed in the presence of catalyst in a Stille-type reaction to give coupled product 10, which is hydrolyzed to give compound 11. Treatment of 11 with, for example, diphenyl phosphoryl azide followed by heat, produces an intermediate isocyanate 11b, which will spontaneously cyclize under the reaction conditions to give compound 12. Treatment of 12 with a chlorinating

15 agent gives chloro compound 19, which may be reacted with suitable primary amines (R_2-NH_2) to give compounds of formula 1c.

Scheme IIIa

Reagents 8 and 9 for Scheme III above may be prepared as shown in Scheme IIIa. Substituted 3-amino-2-naphthoic acids 8a may be converted to substituted 3-iodo-2-naphthoic acids 8b by, for example, diazotization followed by treatment with an iodide salt. Esterification of compound 8b produces 3-iodo-2-naphthoic acid esters 8. 4-Substituted pyrazoles 9a may be treated with a p-toluenesulfonating agent, such as p-toluenesulfonyl chloride, to give p-toluenesulfonamide 9b. Deprotonation of compound 9b with a strong base, such as t-butyl lithium, and treatment with a stannylating agent, such as trimethyl chloro stannane, gives reagent 9.

Scheme IV

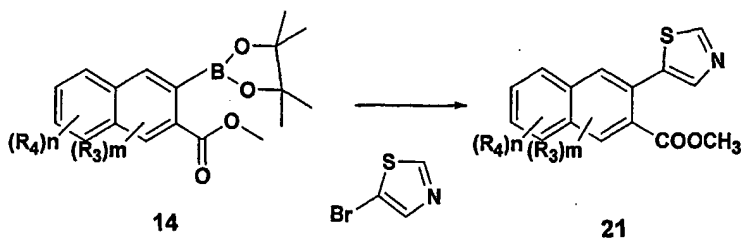
Benzo-imidazo-quinolines

10

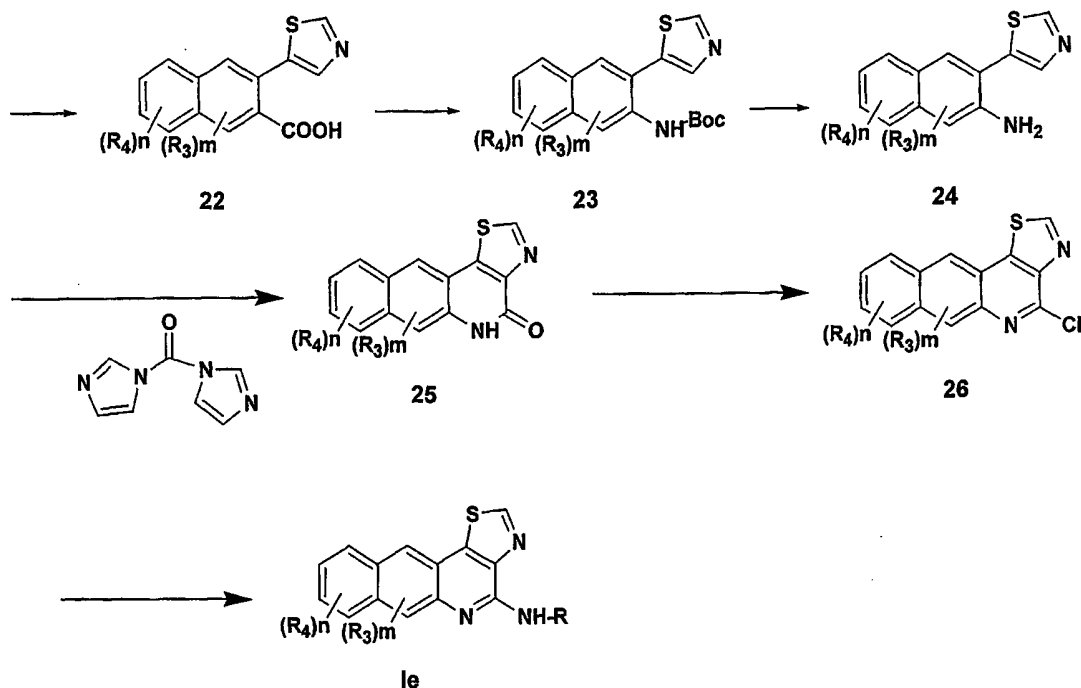
Benzo-imidazo-quinolines of formula Id (wherein X of formula I is NR₁ and R₁ is methyl) may be prepared as shown in Scheme IV. Substituted 3-iodo-2-naphthoic acid esters 8 prepared as in Scheme IIIa are converted to boronate derivatives 14 using catalyst and a reagent such as bis(pinacolato)diboron.

Condensation of compound 14 with 1-methyl-5-bromimidazole and catalyst in a Suzuki-type reaction gives coupled ester 15. Ester 15 is hydrolyzed to give acid 16, which is converted via treatment with diphenylphosphoryl azide (through an intermediate isocyanate -- see 11b) and t-butanol into protected amine 17. Acid treatment converts 17 to free amine 18, which is heated in a high-boiling point inert solvent such as 1,2-dichlorobenzene with carbonyldiimidazole to give cyclized product 19. Treatment with a chlorinating agent converts compound 19 to the chloro derivative 20, which may be converted by treatment with suitable primary amines (R_2-NH_2) to give compounds of formula Id.

10

Scheme VBenzo(g)thiazolo(4,5-c)quinolines

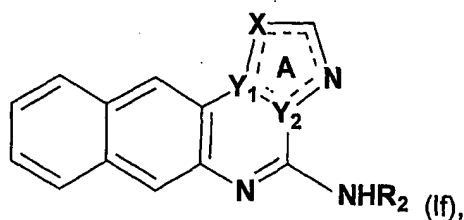
15



- 5 Benzo-thiazolo-quinolines may be prepared as shown above in Scheme V. Substituted 3-boronato-2-naphthoic acid ester **14** is condensed with 5-bromothiazole in a Suzuki-type reaction, catalyzed by a metal such as Pd, to give coupled product **21**. The ester **21** is hydrolyzed under standard conditions to give acid **22**, which is then converted via treatment with diphenylphosphoryl azide (through an intermediate isocyanate similar to 11b) and t-butanol into the protected amine **23**. Acid treatment can convert compound **23** to the free amine **24**, which is heated in a high-boiling inert solvent such as 1,2-dichlorobenzene with carbonyldiimidazole to give cyclized product **25**. Compound **25** may be converted to the chloro derivative **26** by treatment with a chlorinating agent, and
- 10 compound **26** is converted by treatment with suitable primary amines (R_2-NH_2) to give the compound of formula **1e**.

Preferred Compounds

Preferred compounds of this invention are those having the formula (If):



10 and pharmaceutically-acceptable salts thereof, wherein

X is NR₁, CR₁, or S;

Y₁ and Y₂ are nitrogen or carbon, provided that

15 a) when X is CR₁, one of Y₁ and Y₂ is nitrogen, and b) when one of Y₁ and Y₂ is carbon, either the other of Y₁ and Y₂ is nitrogen or X is NR₁ or S, so that ring A defines a five-membered heteroaryl ring having two heteroatoms;

R₁ is hydrogen, halogen, lower alkyl, or substituted lower alkyl;

R₂ is alkyl or substituted alkyl.

20 More preferred are the compounds of formula (If), above, and/or pharmaceutically acceptable salts thereof, wherein

X is NR₁ or CR₁;

R₁ is hydrogen, halogen, lower alkyl, or trifluoromethyl;

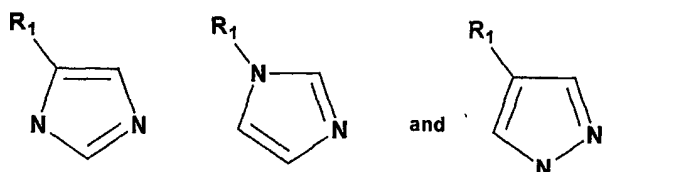
R₂ is C₁₋₂ alkyl optionally substituted with OR₉ or NR₁₀R₁₁;

25 R₉ is hydrogen or lower alkyl; and

R_{10} and R_{11} are (i) independently selected from hydrogen, C_{1-2} alkyl, C_{1-2} substituted alkyl, and $-(C=O)C_{1-2}$ alkyl, or alternatively (ii) together form a five to six membered heterocycle or heteroaryl.

- 5 Most preferred are the compounds of formula (If), above, and/or pharmaceutically acceptable salts thereof, wherein

ring A is selected from:



R_1 is hydrogen, halogen, ethyl, methyl, or trifluoromethyl; and

- 10 R_2 is a C_{1-2} alkyl optionally substituted with one of:

OH, NH_2 , $NH(C_{1-2}alkyl)$, $N(C_{1-2}alkyl)_2$, $NH(C_{1-2}substituted\ alkyl)$, $N(C_{1-2}substituted\ alkyl)_2$, $NH(C=O)C_{1-2}alkyl$, and piperidinyl.

- Advantageously, R_1 does not include hydroxy or an alkyl substituted with
15 hydroxy.

Utility

- The compounds and compositions of this invention are useful in treating conditions that are characterized by release of $NF-\kappa B$ and/or enhanced levels of $TNF-\alpha$. The term "treating" or "treatment" denotes prevention, partial alleviation,
20 or cure of the disease. Inhibition or suppression of $NF-\kappa B$ and/or $TNF-\alpha$ may occur locally, for example, within certain tissues of the subject, or more extensively throughout the subject being treated for such a disease. Inhibition or suppression of $NF-\kappa B$ and/or $TNF-\alpha$ may occur by one or more mechanisms, e.g., by inhibiting or suppressing any step of the pathway(s) such as inhibition of
25 IKK. The term "NF- κB -associated condition" refers to diseases that are

characterized by release of NF- κ B from the cytoplasm (e.g., upon phosphorylation of I κ B). The term "TNF- α -associated condition" is a condition characterized by enhanced levels of TNF- α . In the instant specification, the term NF- κ B-associated condition will include a TNF- α -associated condition but is not
5 limited thereto as NF- κ B is involved in the activity and upregulation of other pro-inflammatory proteins and genes. The term "inflammatory or immune diseases or disorders" is used herein to encompass both NF- κ B-associated conditions and TNF- α -associated conditions, e.g., any condition, disease, or disorder that is associated with release of NF- κ B and/or enhanced levels of TNF- α , including
10 each of the conditions specifically referenced below.

The inventive compounds and compositions are useful for treating a variety of diseases including, but not limited to, treatment of transplant rejections (e.g., kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts and heterografts, etc.); rheumatoid arthritis, psoriatic
15 arthritis, multiple sclerosis, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); antiviral and autoimmune diseases including herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV), Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, and
20 autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); Alzheimer's, Parkinson's, and Creutzfeldt-Jacob diseases; septic shock; hematopoiesis; inflammatory diseases such as osteoarthritis, acute pancreatitis, and chronic pancreatitis; inflammatory disorders of the central nervous system, including HIV encephalitis, cerebral malaria, and meningitis,
25 atherosclerosis, and ataxia telangiectasis; respiratory allergies including asthma, hayfever, and allergic rhinitis; psoriasis, glomerulonephritis, serum sickness, lupus (systemic lupus erythematosus), urticaria, scleraclerma, contact dermatitis, dermatomyositis, alopecia, atopic eczemas, ichthyosis; and fungal infections such as mycosis fungoides. The inventive compounds are also

effective in treating oncological diseases, in treating cancer and tumors, such as solid tumors, lymphomas and leukemia, and in particular, breast cancer, prostate cancer, and Hodgkin's lymphoma.

The present invention thus provides methods for treating such
5 conditions, comprising administering to a subject in need thereof an effective amount of at least one compound of formula I or a salt thereof. Other therapeutic agents such as those described below may be employed in combination with the compounds of formula I. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or
10 following the administration of the inventive compound.

The present invention also provides pharmaceutical compositions capable of treating conditions that are related to the activity of NF- κ B, TNF- α , and/or enzymes modulating NF- κ B and/or TNF- α levels such as IKK. The inventive compositions may contain other therapeutic agents and may be
15 formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

20 The compounds of formula I may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are
25 contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; buccally; parenterally, such as by subcutaneous,

intravenous, intramuscular or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit
5 formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous
10 implants or osmotic pumps.

Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk,
15 alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents
20 and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight
25 excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ®); and agents to

control release such as polyacrylic copolymer (e.g., CARBOPOL 934®).

Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration
5 include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable
10 solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

15 Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

20 The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood
25 that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the

subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like, subject NF- κ B and/or TNF- α associated conditions.

The inventive compounds and compositions may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in treating NF- κ B and TNF- α associated conditions. Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, CSAIDs, 4-substituted imidazo [1,2-A]quinoxalines as disclosed in US Pat. No. 4,200,750 and Ceccarelli *et al.*, *supra*; Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathioprine and cyclophosphamide; TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof; and other cancer drugs and treatments, including radiation treatments and daunorubicin.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Assays

TNF α Production

THP-1 (human monocytic cell line) obtained from ATCC was cultured in RPMI-1640 supplemented with 10% FBS, sodium pyruvate, HEPES, 2-

mercaptoethanol, Penicillin/Streptomycin. To a 96-well plate containing THP-1 cells (1.4×10^6 /mL, 2.5×10^5 cells/well) in 180 μ L RPMI-1640 was added 20 μ L of the test compound in 10% DMSO. Typically, test compound concentrations of 0.1-100 μ M were used in the assay. After one hour at 37°C, 20 μ L of 1000
5 ng/mL lipopolysaccharide (LPS from *Salmonella typhosa*, Sigma) was added to each well. After an additional 6 hours at 37°C, the supernatants were collected following a 5 minute centrifugation of the plate to pellet the cells. The amount of TNF α in these supernatants was then measured using a TNF α -specific ELISA (Pharmingen). After subtracting out the amount of TNF α in a control that had not
10 been treated with LPS, the percent inhibition was calculated versus a control that was treated with LPS but with no test compound added. IC₅₀ values were calculated from the percentage inhibition at various doses. Compounds of Examples 1-8 demonstrated IC₅₀ values of below 9 μ M, with preferred and more preferred compounds having IC₅₀ values of below 2 μ M and 1 μ M, respectively.
15

TNF α -Stimulated Degradation of I κ B α in THP-1 cells

TNF α stimulation of monocytic THP-1 cells leads to the proteolytic degradation of I κ B α . Both an IKK-dependent phosphorylation and ubiquitin ligase-dependent ubiquitination of I κ B α are essential steps in the TNF α -
20 stimulated pathway targeting I κ B α for proteolytic degradation by the proteasome. THP-1 cells were suspended in RPMI-1640 supplemented with 10% fetal bovine serum, preincubated for 60 mins with test agent, then stimulated for 15 mins with TNF α (100 ng/mL, R&D Systems). Total cell lysates were fractionated by sodium dodecylsulfate-polyacrylamide electrophoresis followed by Western blot
25 analysis. I κ B α was detected using a polyclonal antibody from Santa Cruz (catalog #sc-4094) and ECL reagents (Amersham). Films were scanned using a Kodak ID Image Analysis system to quantitate the amount of I κ B α . Compounds of formula (I) demonstrate up to 100% inhibition of the TNF α -induced degradation of I κ B α in THP-1 cells at 10 μ M.

LPS-Induced Serum TNF α in Mice

As a measure of activity against NF- κ B-dependent TNF α production *in vivo*, test compounds were administered to BALB/c mice subsequently challenged with an intravenous dose of *E. coli* LPS (1 μ g in 100 μ L phosphate-buffered saline). 1 hour after LPS challenge, blood was collected from the mice and the levels of TNF α in the serum measured by EIA (R&D Systems). Inhibition was calculated from control animals which received LPS challenge with no test compound. Compounds of formula (I) demonstrated inhibition of the LPS-induced serum TNF α levels *in vivo* in the range of about 30 to 65% at 10 mg/kg, p.o.; in the range of about 70 to 90% at 30 mg/kg p.o.; and in the range of above 90% at 100 mg/kg p.o.

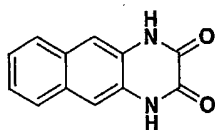
Accordingly, compounds of formula (I) have been tested and shown activity as inhibitors of TNF- α and the NF- κ B pathway.

The following Examples illustrate embodiments of the invention and are not intended to limit the scope of the claims. The reagents and starting materials of Preparations 1-19 are useful in synthesizing compounds of formula I, or salts thereof, such as illustrated in Schemes I-V. In the following Examples, anhydrous reactions were performed under an atmosphere of nitrogen or argon using either commercially available dry solvents or freshly distilled solvents. Melting points were determined in an open capillary tube with a Thomas-Hoover melting point apparatus. Column chromatography was performed using EM Science silica gel 60 (230-400 mesh) with the designated solvent system as eluant. Thin-layer chromatography was done on E. Merck silica gel 60 F₂₅₄ plates (0.5 mm). HPLC purity determinations were done using either an HP 1090 DR5 with a diode array detector and a Waters Nova-Pak C18 column (3.9 x 150 mm), or a Shimadzu LC-10AS with a SPD-10AV UV-Vis detector and one of the following columns: YMC Combiscreen ODS-A (4.6 x 50 mm); HP Zorbax SB-C18 (4.6 x 750 mm). Infrared spectra and ¹HNMR spectra were recorded and

chemical shifts are expressed in parts per million (ppm or δ) with the solvent in use as internal standard. Coupling constants are given in Hertz and multiplets are designated as follows; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low resolution mass spectra were determined on a Finnigan
5 Matt TSQ-7000 triple stage quadrupole spectrometer (positive/negative ESI) operated in the negative ion mode.

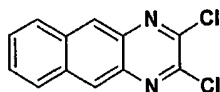
Preparation of Reagents and Starting Materials

10 Preparation 1 1,4-Dihydrobenzo[g]quinoxalin-2,3-dione



A mixture of 2,3-diaminonaphthalene (2.87 g, 18.14 mmol) and diethyl
15 oxalate (30 mL, 223 mmol) was heated to reflux for 14 hours, cooled to RT and filtered. The residue was washed with EtOH and dried *in vacuo* to give the title compound as a brown solid (3.15 g, 82%); mp > 350 °C; IR (KBr, cm^{-1}) 3045, 2942, 2869, 1716, 1642, 1406, 877; ^1H NMR (DMSO) δ 12.11 (s, 2H), 7.84-7.81 (m, 2H), 7.54 (s, 2H) 7.39 (dd, J = 6.3, 3.0, 2H); LC/MS 92.5% (220 nm), m/z (M
20 + H^+) 213.

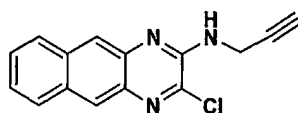
Preparation 2 2,3-Dichlorobenzo[g]quinoxaline



1 g (4.72 mmol) of 1,4-dihydrobenzo[g]quinoxalin-2,3-dione was stirred in 2 ml of phosphorus oxychloride for 5 hours at reflux. The mixture was concentrated by evaporation and dried under high vacuum. A sat'd K₂CO₃ solution was carefully added to the residue, and the solid was filtered off and washed with water to afford the title compound as a brown solid (1.00 g, 85%); mp 239-242 °C; IR (KBr, cm⁻¹) 1200, 1109, 998, 886, 748; ¹H NMR (DMSO) δ 8.78 (s, 2H), 8.31-8.28 (m, 2H), 7.75-7.73 (m, 2H).

10

Preparation 3
2-Chloro-3-(propargylamino)benzo[g]quinoxaline

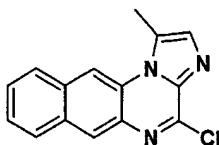


15

A mixture of 2,3-dichlorobenzo[g]quinoxaline (0.634 g, 2.55 mmol), propargylamine (0.21 ml, 3.05 mmol) and TEA (0.53 mL, 3.83 mmol) in 15 mL of dioxane was heated to reflux for 4.5 hours. After evaporating the resulting mixture under vacuum, the crude product was chromatographed (CH₂Cl₂) to afford the title compound as a yellow solid (0.496 g, 73%); mp 169-172 °C; IR (KBr, cm⁻¹) 3412, 3283, 3235, 1570, 1508, 1335; ¹H NMR (DMSO) δ 8.44 (s, 1H), 8.26 (s, 1H), 8.16-8.06 (m, 3H), 7.58-7.54 (m, 1H), 7.51-7.48 (m, 1H), 4.28 (dd, J = 6.1, 2.5, 2H), 3.12 (t, J = 2.5, 1H); LC/MS 97.8% (220 nm), m/z (M + H⁺) 268.

25

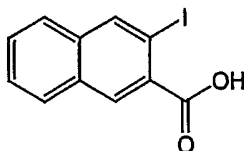
Preparation 4
4-Chloro-1-methylbenzo[g]imidazo[1,2-a]quinoxaline



30

2-Chloro-3-(propargylamino)benzo[g]quinoxaline (0.420 g, 1.57 mmol) was treated with 4 mL of concentrated H₂SO₄ and the mixture was stirred at 80 °C for 1 hour, cooled to RT and poured into ice water. The mixture was cautiously neutralized with aqueous NaOH, and the resulting precipitate was filtered, washed with water, and dried *in vacuo* to give the title compound as a beige solid (0.124 g, 30%); mp 221-223° C; IR (KBr, cm⁻¹) 1538, 1479, 1456, 1398, 1101, 919; ¹H NMR (DMSO) δ 8.79 (s, 1H), 8.53 (s, 1H), 8.23 (d, J = 8.1, 1H), 8.13 (d, J = 8.5, 1H), 7.69-7.59 (m, 3H), 3.04 (s, 3H); LC/MS 100% (220 nm), m/z (M + H⁺) 268.

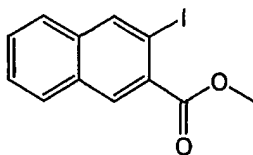
Preparation 5
3-Iodo-2-napthoic acid



To a beaker of 3-amino-2-napthoic acid (6.01 g, 80% pure; 25.69 mmol), was added a solution of concentrated HCl (10.0 mL) and water (15.0 mL). After the resulting pink paste was stirred for 17 min, it was cooled to 0°C and treated with a solution of water (10 mL) and NaNO₂ (2.54 g, 36.81 mmol) drop-wise (over 8 min). One minute later, the brown reaction mixture was treated with a cooled (0°C) water (10.0 mL) solution of KI (10.0 g, 60.24 mmol) drop-wise (over 12 min). The cooling bath was removed, water (15 mL) was added, and the reaction mixture was stirred for 10 min at RT and heated at 95°C for 65 min. It was then diluted with water (50 mL) and extracted with EtOAc (250 mL). The organic layer was washed with water (50 mL) and brine, dried (MgSO₄), filtered, and

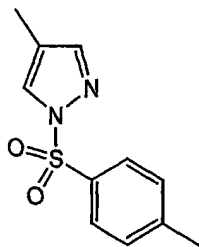
evaporated *in vacuo*. The resultant crude material was submitted to flash chromatography (sample was loaded as a silica gel mesh; EtOAc) to afford the title compound as an iodine colored fluffy solid weighing ~6.50 g. ¹H NMR (DMSO, δ = 2.50): 13.36 (br s, 1H), 8.63 (s, 1H), 8.37 (s, 1H), 8.05 (d, J = 7.9, 1H), 7.93 (d, J = 8.0, 1H), 7.67-7.60 (m, 2H).

Preparation 6
Methyl 3-iodo-2-napthoate



To 3-iodo-2-napthoic acid (Preparation 5) (6.50 g), were added MeOH (100 mL) and concentrated H₂SO₄ (2 mL), and the resultant heterogeneous mixture was refluxed for 13 hr. The reaction mixture was allowed to cool to RT, then neutralized with NaHCO₃ (6.0 g), and the volatile component was removed *in vacuo*. The residue was partitioned between water (50 mL) and EtOAc (300 mL). The organic layer was washed with Na₂S₂O₃ solution (4.2 g + 50 mL of water) and brine, dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting crude material was submitted to flash chromatography (sample was loaded as a silica gel mesh, 10% EtOAc/hexanes) to isolate the title compound as a light-yellow solid (5.50g, 2 steps combined yield of 69%). ¹H NMR (DMSO, δ = 2.50): 8.66 (s, 1H), 8.39 (s, 1H), 8.06 (d, J = 8.0, 1H), 7.95 (d, J = 8.0, 1H), 7.69-7.62 (m, 2H), 3.91 (s, 3H). (DCI) m/z (M+H)⁺ = 313.0. Anal. Calcd for C₁₂H₉IO₂: C, 46.18; H, 2.91. Found: C, 46.28; H, 2.85.

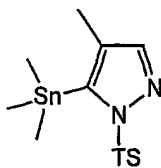
Preparation 7
4-Methyl-1-(4-tolunesulfonyl)pyrazole



p-TsCl (9.81g, 51.46 mmol) was added in batches over a few minutes to a
 5 CH₂Cl₂ (100 mL) solution of 4-methylpyrazole (4.00 g, 48.72 mmol) and pyridine
 (6.0 mL, 74.18 mmol). The reaction mixture was stirred for 95 min, then diluted
 with CH₂Cl₂ (250 mL) and washed with NaHCO₃ solution [a mixture of sat'd
 NaHCO₃ solution (20 mL) and H₂O (40 mL)], and water (60 mL). The organic
 layer was dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting crude
 10 material was purified by flash chromatography (sample was loaded as a silica gel
 mesh; CH₂Cl₂) to afford the title compound as a white solid (10.88 g, 95%). ¹H
 NMR (CDCl₃, δ = 7.26): 7.87 (d, J = 8.4, 2H), 7.84 (s, 1H), 7.54 (s, 1H), 7.32 (d, J
 = 8.40, 2H), 2.41 (s, 3H), 2.06 (s, 3H). (ESI) m/z (M+H)⁺ = 236.7. Anal. Calcd for
 C₁₁H₁₂N₂O₂S: C, 55.91; H, 5.12; N, 11.86. Found: C, 55.81; H, 4.94; N, 11.76.

15

Preparation 8
4-Methyl-1-(4-toluenesulfonyl)-5-trimethylstannylpyrazole



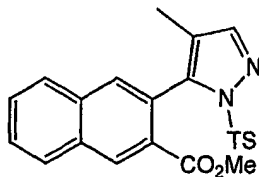
20

t-BuLi (1.7 M/pentane) was added over 10 min to a cooled (-78 °C) THF
 (60 mL) semi-suspension of 4-methyl-1-(4-toluenesulfonyl)pyrazole (Preparation
 7) (6.01 g, 25.43 mmol). After the mixture was stirred for 10 min, it was treated
 25 drop-wise (over 20 min) with Me₃SnCl (28.0 mL of 1.0 M/THF, 28.0 mmol). The

resulting mixture was stirred for 4.3 hr while the bath was allowed to thaw to -55°C , and then for 70 min. at RT. The reaction mixture was diluted with EtOAc (250 mL) and washed with water (50 mL) and brine, dried (MgSO_4), filtered, and evaporated *in vacuo*. The crude material was submitted to flash chromatography (sample was loaded as a silica gel mesh; 15-20% EtOAc/hexanes) to afford the title compound as a dense white solid (4.406 g, 43%). Non-consumed pyrazole of Preparation 7, above, was also retrieved (1.954 g, 33%). ^1H NMR of the title compound (DMSO , $\delta = 2.50$): 7.74 (s, 1H), 7.70 (d, $J = 8.3$, 2H), 7.45 (d, $J = 8.3$, 2H), 2.38 (s, 3H), 2.08 (s, 3H; satellite peaks due to Sn-H with $J = 4.5$), 0.45 (s, 9H; satellite peaks due to Sn-H with $J = 59.8$ and 57.3). (ESI) m/z ($\text{M}+\text{H}$) $^+ = 400.9$.

Preparation 9

Methyl 3-(4-methyl-1-(4-toluenesulfonyl)pyrazol-5-yl)-2-naphthoate

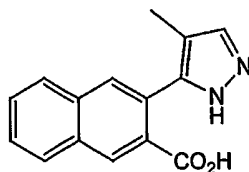


DMF (26.0 mL) was added into a mixture of methyl-3-iodo-2-naphthoate (Preparation 6) (2.017 g, 6.463 mmol), 4-methyl-1-(4-toluenesulfonyl)-5-trimethylstannylpyrazole (Preparation 8) (2.895 g, 7.254 mmol), Pd_2dba_3 (236 mg, 0.258 mmol), Ph_3As (317.2 mg, 1.036 mmol), and CuI (130.7 mg, 0.686 mmol). After nitrogen was bubbled through the heterogeneous mixture for a few minutes, it was stirred at RT for 7 min and at 90°C for 12 hr. The volatile component was removed *in vacuo*, and the resultant viscous residue was submitted to flash chromatography (sample was loaded as a silica gel mesh; 0-10 % EtOAc/ CH_2Cl_2) to afford the titled compound as a yellow solid (1.485 g,

55%). ^1H NMR (DMSO, δ = 2.50): 8.73 (s, 1H), 8.23 (d, J = 7.7, 1H), 8.05 (d, J = 7.7, 1H), 7.83 (s, 1H), 7.81 (s, 1H), 7.77-7.71 (m, 2H), 7.50 (d, J = 8.2, 2H), 7.38 (d, J = 8.2, 2H), 3.66 (s, 3H), 2.38 (s, 3H), 1.77 (s, 3H). (ESI) m/z ($M+H$) $^+$ = 421.0.

5

Preparation 10
3-(4-Methylpyrazol-5-yl)-2-naphthoic acid

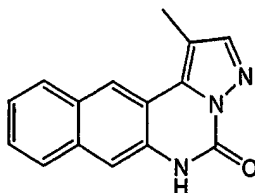


10

THF (12.0 mL), MeOH (8.0 mL) and NaOH solution (7.5 mL of 1.0 N/H₂O) were added to methyl-3-(4-methyl-1-(4-toluenesulfonyl)pyrazol-5-yl)-2-naphthoate (Preparation 9) (1.240 g, 2.949 mmol), and the reaction mixture was heated at 80°C for 4.2 hr. It was then diluted with water (20 mL), acidified to pH ~ 4.5 with 15 1N HCl, and extracted with EtOAc (75 mL, 2x). The combined organic layer was washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo*. The resulting crude material was submitted to flash chromatography (sample was loaded as a silica gel mesh; 10% MeOH/CH₂Cl₂) to isolate the title compound as faint-yellow solid (300 mg, 40%). ^1H NMR (DMSO, δ = 2.50; one tautomer was 20 observed): 12.70 (br s, 2H), 8.37 (s, 1H), 8.08 (d, J = 7.9, 1H), 8.01 (d, J = 8.0, 1H), 7.93 (s, 1H), 7.65-7.58 (m, 2H), 7.47 (s, 1H), 2.01 (s, 3H). (ESI) m/z ($M+H$) $^+$ = 252.99.

25

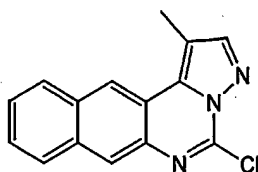
Preparation 11
1-Methylbenzo(g)pyrazolo(1,5-c)quinazolin-5-one



Et₃N (300 μ L, 2.152 mmol) and (PhO)₂PON₃ (440 μ L, 2.064 mmol) were added to a C₆H₆ (10.0 mL) suspension of 3-(4-methylpyrazol-5-yl)-2-naphthoic acid (Preparation 10) (257 mg, 1.019 mmol), and the mixture was heated at 50°C for 2 hr. The volatile component was removed *in vacuo*, and the resulting yellow solid was dissolved in *o*-dichlorobenzene (8.0 mL) and heated at 150°C for 4 hr. During the latter heating, there was a gradual evolution of gas accompanied by the formation of a suspension. The reaction mixture was allowed to cool to RT, and the precipitate was filtered and washed with copious ether to afford the title compound as a fluffy light-yellow solid (170.8 mg, 67%). ¹H NMR (DMSO, δ = 2.50): 11.86 (s, 1H), 8.57 (s, 1H), 8.13 (d, J = 8.2, 1H), 7.99 (s, 1H), 7.92 (d, J = 8.3, 1H), 7.22 (s, 1H), 7.56 (app t, J = 7.21, 1H), 7.49 (app t, J = 7.48, 1H), 2.60 (s, 3H). (ESI) m/z (M+H)⁺ = 250.00.

15

Preparation 12
1-Methyl-5-chlorobenzo(g)pyrazolo(1,5-c)quinazoline

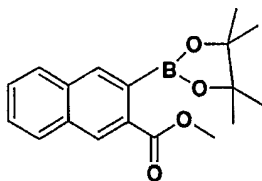


20

PhNEt₂ (1.50 mL) and POCl₃ (15.0 mL) were added to 1-methylbenzo(g)pyrazolo(1,5-c)quinazolin-5-one (Preparation 11) (184.7 mg,

0.741 mmol), and the resulting heterogeneous mixture was heated at reflux for 46 hr. During heating, the suspension (the starting material), gradually started to dissolve. The dark-green reaction mixture was filtered to remove non-consumed starting material (16.2 mg, 8.8%), and the filtrate was exposed to high vacuum to remove most of the POCl_3 . The residue was partitioned between water (30 mL) and EtOAc (70 mL). The organic layer was washed with brine, dried (MgSO_4), filtered, and evaporated *in vacuo*. The crude material was submitted to flash chromatography (sample was loaded as a silica gel mesh; 20% EtOAc/hexanes) to afford the title chloride as an off-white solid (153 mg, 77%). ^1H NMR (DMSO , δ = 2.50): 8.80 (s, 1H), 8.46 (s, 1H), 8.29-8.27 (m, 1H), 8.19 (s, 1H), 8.17-8.15 (m, 1H), 7.70-7.65 (m, 2H), 2.70 (s, 3H). (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 267.98.

Preparation 13

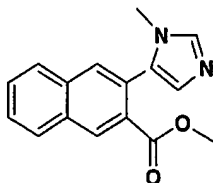
Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthoate

To a solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (30.0 g, 0.118 mol) and methyl 3-iodo-2-naphthoate (Preparation 6) (33.5 g, 0.107 mol) in DMSO (600 mL) were added $\text{PdCl}_2(\text{dppf})$ (2.62 g, 0.21 mmol) and KOAc (31.51 g, 0.321 mol). The mixture was degassed and purged with N_2 , and then heated at 85°C for 18 hours. The brown reaction mixture was cooled to RT, diluted with water (1.5 L), and extracted with EtOAc (2.5 L, then 2x500 mL). The combined organic layer was washed with brine (9x500 mL), dried over MgSO_4 , filtered and evaporated *in vacuo*. The resulting crude material was submitted to flash chromatography (2.0% $\text{MeOH}/\text{CHCl}_3$), affording the title compound as a

yellow solid (19.5 g, 58%). ^1H NMR (CDCl_3): 8.50(s, 1H), 7.99(s, 1H), 7.90(d, $J=8.1$, 1H), 7.86(d, $J=8.1$, 1H), 7.57(m, 1H), 7.54(m, 1H), 3.98(s, 3H), 1.47(s, 12H). (ESI) m/z ($M+H$) $^+$ = 313.16

5

Preparation 14
Methyl-3-(1-methyl-imidazol-5-yl)-2-naphthoate

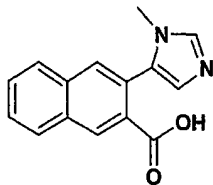


10

To a mixture of methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthoate (Preparation 13) (15.37 g, 49.3 mmol) and 5-bromo-1-methyl-1H-imidazole (9.06 g, 49.3 mmol) in toluene/EtOH (350 mL/36 mL) were added Pd(PPh_3) $_4$ (11.37 g, 9.84 mmol), Na_2CO_3 (20.9 g, 197.2 mmol) and water (106 mL). The mixture was degassed, purged with N_2 , and heated to reflux for 20 hours. It was then cooled to RT, neutralized with HCl (1.0 N, 100 mL), and concentrated *in vacuo*. The residue was partitioned between water (300 mL) and EtOAc (1 L). The organic layer was washed with water (2 L) and brine, dried over MgSO_4 , filtered and evaporated *in vacuo*. The resulting crude material was submitted to flash chromatography (1.5% MeOH/ CHCl_3), furnishing the title compound as a light-yellow solid (9.5 g, 72%). ^1H NMR(CDCl_3): 8.53(s, 1H), 7.99(d, $J=8.1$, 1H), 7.80(d, $J=8.1$, 1H), 7.77(s, 1H), 7.56(m, 1H), 7.54(m, 1H), 7.54(s, 1H), 6.94(s, 1H), 3.73(s, 3H), 3.29(s, 3H). (ESI) m/z ($M+H$) $^+$ = 267.11.

25

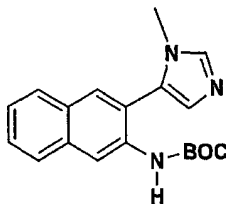
Preparation 15
3-(1-Methyl-imidazol-5-yl)-2-naphthoic acid



A solution of methyl-3-(1-methyl-imidazol-5-yl)-2-naphthoate (Preparation
5 14) (8.5 g, 32 mmol) in THF/MeOH (3/2, 120 mL) was treated with aqueous
NaOH (1.0 N, 48 mL). After 20 hours at RT, it was neutralized with aqueous HCl
(1.0 N, 20 mL). The solvent was evaporated *in vacuo*. The solid residue was
treated with MeOH (5 mL), then evaporated again. The resulting crude material
was purified by flash chromatography (5% MeOH/EtOAc) affording the title
10 compound as a pale-yellow solid (6.0 g, 74%). ¹H NMR(CDCl₃): 8.34(s, 1H),
7.95(d, J=8.1, 1H), 7.90(d, J=8.1, 1H), 7.72(s, 1H), 7.53(s, 1H), 7.52(m, 1H),
7.50(m, 1H), 6.83 (s, 1H), 3.16(s, 3H). (ESI) m/z (M+H)⁺ = 253.10.

Preparation 16

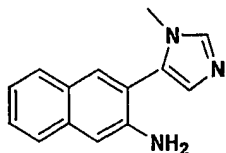
15 1,1-Dimethylethyl-3-((1-methylimidazol-5-yl)-2-naphthyl)carbamate



To a mixture of 3-(1-methyl-imidazol-5-yl)-2-naphthoic acid (Preparation
20 15) (1.0 g, 3.95 mmol) and Et₃N (1.1 mL, 7.91 mmol) in 20ml *t*-BuOH was added
diphenylphosphoryl azide (1.63 g, 5.93 mmol). After 40 minutes at 80°C, the
mixture was cooled to RT. The slurry was diluted with EtOAc (300 mL), and

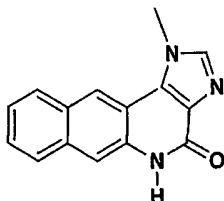
washed once with water (50 mL) and three times with brine. The organic layer was dried over MgSO_4 , filtered, and evaporated *in vacuo*. The crude material was submitted to flash chromatography (0.5% MeOH/EtOAc) affording the title compound as a pale-yellow solid (0.67 g, 51%). ^1H NMR(CDCl_3): 8.34(s, 1H), 7.95(d, $J=8.1$, 1H), 7.90(d, $J=8.1$, 1H), 7.72(s, 1H), 7.53(s, 1H), 7.52(m, 1H), 7.50(m, 1H), 6.83 (s, 1H), 3.16(s, 3H), 1.43(s, 9H). (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 324.15

Preparation 17
5-(3-Amino-2-naphthyl)-1-methylimidazole



A solution of 1,1-dimethylethyl-3-((1-methylimidazol-5-yl)-2-naphthyl)carbamate (Preparation 16) (1.0 g, 2.98 mmol) in TFA/ CH_2Cl_2 (1:10, 50 mL) was stirred at RT for 18 hours. After concentration, the residue was diluted with EtOAc (200 mL), washed with aqueous NaHCO_3 (100 mL) and brine. The organic layer was then dried over MgSO_4 , filtered and evaporated *in vacuo*. The crude material was submitted to flash chromatography (5% MeOH/EtOAc) affording the title compound as a light yellow solid (0.49 g, 70%). ^1H NMR(CDCl_3): 7.65(d, $J=8.1$, 1H), 7.59(d, $J=8.1$, 1H), 7.57(s, 1H), 7.56(s, 1H), 7.36(m, 1H), 7.22(m, 1H), 7.13(s, 1H), 7.03 (s, 1H), 3.96(b, 2H), 3.46(s, 3H). (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 224.08

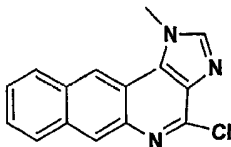
Preparation 18
1-Methyl-4,5-dihydrobenzo(g)imidazo(4,5-c)quinolin-4-one



A mixture of 5-(3-amino-2-naphthyl)-1-methylimidazole (Preparation 17) (0.48 g, 2.14 mmol) and 1,1'-carbonyldiimidazole (0.42 g, 2.57 mmol) in *o*-dichlorobenzene (22 mL) was heated at 180°C for 5 hours. The suspension was cooled to RT, filtered, and dried under vacuum, affording the title compound as a light yellow solid (0.22 g, 42%). ¹H NMR(DMSO): 11.57(s, 1H), 8.71(s, 1H), 8.15(s, 1H), 8.10(d, J=8.4, 1H), 7.89(d, J=8.4, 1H), 7.84(s, 1H), 7.53(m, 1H), 7.46(m, 1H), 4.30(s, 3H). (ESI) *m/z* (M+H)⁺ = 250.08.

10

Preparation 19
1-Methyl-4-chlorobenzo(g)imidazo(4,5-c)quinoline



15

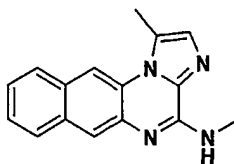
To a mixture of 1-methyl-4,5-dihydrobenzo(g)imidazo(4,5-c)quinolin-4-one (Preparation 18) (200 mg, 0.80 mmol) and PhNEt₂ (2.5 mL, 1.6 mmol) was added POCl₃ (8 mL). The mixture was then heated to reflux for 4 hours. After cooling, excess POCl₃ was removed under vacuum. The residue was diluted with EtOAc (150 mL), and treated with NaHCO₃ (1 g) to neutralize the acid. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude material was submitted to flash chromatography (EtOAc) affording the title compound as a light yellow solid (0.18 g, 90%). ¹H

20

NMR(CDC₃): 8.61(s, 1H), 8.57(s, 1H), 8.01(d, J=8.8, 1H), 7.98(d, J=8.8, 1H), 7.89(s, 1H), 7.57(m, 1H), 7.54(m, 1H), 4.35(s, 3H). (ESI) m/z (M+H)⁺ = 268.08.

5

Example 1

1-Methyl-4-methylaminobenzo[g]imidazo[1,2-a]quinoxaline

10

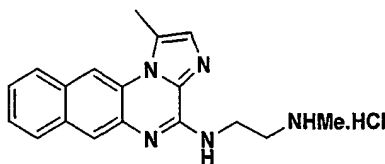
To a solution of 4-chloro-1-methylbenzo[g]imidazo[1,2-a]quinoxaline (0.063 g, 0.236 mmol) (Preparation 4) in 4 mL of THF was added MeNH₂ (40% in H₂O, 0.16 mL, 1.88 mmol). The reaction tube was sealed and the mixture stirred at 80°C for 18 hours. The cooled mixture was then taken up in EtOAc, washed with water and brine, dried (Na₂SO₄) and evaporated. The resulting residue was recrystallized using i-PrOH to give Example 1 as beige needles (0.043 g, 69%); mp 201-202 °C, IR (KBr, cm⁻¹) 3324, 1575, 1557, 1411, 1121; ¹H NMR (DMSO) δ 8.62 (s, 1H), 8.10 (s, 1H), 8.08 (d, J = 8.1, 1H), 7.94 (d, J = 8.1, 1H), 7.77 (br d, J = 4.5, 1H), 7.49-7.45 (m, 2H), 7.35 (s, 1H), 3.06 (d, J = 4.6, 3H), 2.98 (s, 3H); MS (⁺ESI, M + H⁺) m/z 263; HPLC: 99.5% (230 nm); HRMS calcd for C₁₆H₁₄N₄: 262.1219; found 262.1226.

20

Example 2

1-Methyl-4-(2-N-methylaminoethylamino)benzo[g]imidazo[1,2-a]quinoxaline hydrochloride

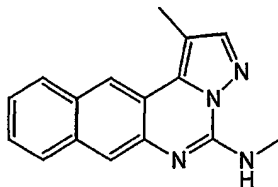
25



To a solution of 4-chloro-1-methylbenzo[g]imidazo[1,2-a]quinoxaline
5 (0.075 g, 0.281 mmol) (Preparation 4) in 4 mL of THF was added
N-methylethylene diamine (0.20 mL, 2.25 mmol). The reaction tube was sealed
and the mixture stirred at 80°C for 18 hours. The resulting cooled mixture was
then taken up in EtOAc, washed with water and brine, dried (Na₂SO₄) and
evaporated. Purifying the residue by preparative TLC (CH₂Cl₂:MeOH, 8:2)
10 yielded 1-methyl-4-(2-*N*-methylaminoethylamino)benzo[g]imidazo[1,2-a]
quinoxaline. This solid was dissolved in CH₂Cl₂/EtOH and a solution of 1N HCl in
EtOH was added to form the hydrochloride salt, which was filtered, washed with
EtOH and dried *in vacuo* to afford the above titled salt as an off-white solid (0.025
g, 26%); mp 265-275 °C dec; IR (KBr, cm⁻¹) 3448, 2958, 2780, 1656, 1532, 1420;
15 ¹H NMR (CD₃OD) 8.72 (s, 1H), 8.42 (s, 1H), 8.13-8.11 (m, 1H), 8.01-7.98 (m,
1H), 7.63-7.57 (m, 3H), 4.23-4.20 (m, 2H), 3.54-3.51 (m, 2H), 3.07 (s, 3H), 2.86
(s, 3H); MS (⁺ESI, M + H⁺) m/z 306; HPLC: 98.3% (230 nm); HRMS calcd for
C₁₈H₁₉N₅: 306.1719; found 306.1708.

20

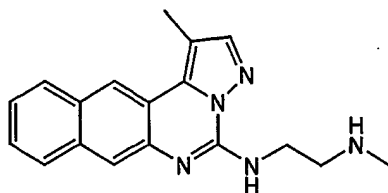
Example 3
1-Methyl-4-methylaminobenzo[g]pyrazolo[1,5-c]quinazoline



25

A mixture of 4-methyl-1-(4-tolunesulfonyl)-5-trimethylstannylpyrazole (Preparation 8) (24.0 mg, 0.0896 mmol) and MeNH₂ (3.0 mL of 2.0 M/THF, 6.0 mmol) in a pressure tube was heated at 60°C for 5 hr. After the reaction mixture was cooled to RT, it was treated with NaHCO₃ (57 mg) and water (2 pipet-drops) and stirred for 5 min. Silica gel was added and the volatile component was removed *in vacuo*. The resulting silica gel mesh was submitted to flash chromatography (20% EtOAc/hexanes) to afford the title compound as a light yellow solid (23.0 mg, 98%). ¹H NMR (DMSO, δ = 2.50): 8.60 (s, 1H), 8.10 (s, d, J = 8.3, 1H), 8.03 (s, 1H), 8.01 (s, 1H), 7.95 (d, J = 8.01, 1H), 7.92 (q, J = 4.7, 1H), 7.50 (t, J = 7.5, 1H), 7.44 (t, J = 7.4, 1H), 3.09 (d, J = 4.7, 3H), 2.66 (s, 3H). (ESI) m/z (M+H)⁺ = 263.02.

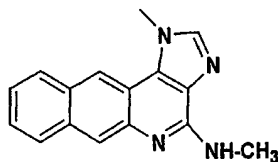
Example 4

1-Methyl-4-(2-N-methylaminoethylamino)benzo[g]pyrazolo[1,5-c]quinazoline

N-methyl-ethylenediamine (250 μ L, 2.836 mmol) was added rapidly to a THF (2.0 mL) semi-suspension of 4-methyl-1-(4-tolunesulfonyl)-5-trimethylstannylpyrazole (Preparation 8) (30.5 mg, 0.114 mmol). The reaction mixture was stirred at RT for 1 hr and at 75°C for 2.3 hr. After the reaction mixture was cooled to RT, it was treated with NaHCO₃ (57 mg) and water (2 pipet-drops) and stirred for a few minutes. The volatile components, including the excess diamine, were removed *in vacuo*. The crude material was submitted to flash chromatography (sample was loaded as a silica gel mesh; 0-100%

MeOH/EtOAc) to afford the title compound as a yellow waxy-solid (43.4 mg; the weight is 8.6 mg more than the theoretical yield). ^1H NMR (DMSO, δ = 2.50): 8.60 (s, 1H), 8.10 (d, J = 8.1, 1H), 8.02 (s, 2H, signal overlap), 7.95 (d, J = 8.1, 1H), 7.73 (t, J = 5.5, 1H), 7.51 (ddd, J = 8.2, 6.8, 1.1, 1H), 7.45 (ddd, J = 8.0, 6.9, 1.0, 1H), 3.66 (apt q, J = 6.1, 2H), 2.82 (t, J = 6.3, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 1.81 (s, 1H). (ESI) m/z ($M+H$) $^+$ = 306.05.

Example 5

1-Methyl-4-methylaminobenzo(g)imidazo(4,5-c)quinoline

10

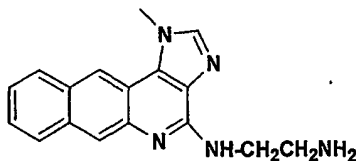
A mixture of 1-methyl-4-chlorobenzo(g)imidazo(4,5-c)quinoline (Preparation 19) (130 mg, 0.49 mmol) and MeNH_2 (2.0M/THF, 1.5 mL, 2.92 mmol) was heated in a pressure tube at 80°C for 18 hours. After the reaction mixture was cooled to RT, it was diluted with EtOAc (100 mL), washed with sat'd NaCO_3 (50 mL), and brine. The organic layer was dried over MgSO_4 , filtered and evaporated *in vacuo*. The crude material was submitted to flash chromatography (5% MeOH/EtOAc) affording the title compound as a pale white solid (5.2 mg, 4%). ^1H NMR(CDCl_3): 8.44(s, 1H), 8.35(s, 1H), 7.94(d, J =8.3, 1H), 7.90(d, J =8.3, 1H), 7.72(s, 1H), 7.46(m, 1H), 7.40(m, 1H), 5.95(b, 1H), 4.28(s, 3H), 3.31(s, 3H). (ESI) m/z ($M+H$) $^+$ = 263.14

20

Example 6

1-Methyl-4-(2-N-methylaminoethylamino)benzo(g)imidazo(4,5-c)quinoline

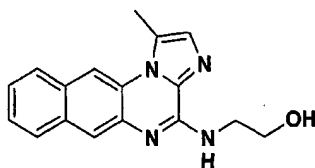
25



A solution of 1-methyl-4-chlorobenzo(g)imidazo(4,5-c)quinoline (Preparation 19) (130 mg, 0.49 mmol) in $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ (3.2 mL, 49 mmol), was heated at 60°C for 18 hours. The solvent was evaporated *in vacuo*. The residue was diluted with EtOAc (50 mL) and washed with brine (20 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated. The crude material was submitted to flash chromatography (MeOH) affording the title compound as a pale white solid (6.9 mg, 5%). ^1H NMR(CDCl_3): 8.52(s, 1H), 8.33(s, 1H), 7.96(d, $J=8.3$, 1H), 7.94(d, $J=8.3$, 1H), 7.77(s, 1H), 7.46(m, 1H), 7.42(m, 1H), 6.22(b, 1H), 4.36(s, 3H), 3.85(m, 2H), 3.10(m, 2H), 1.60(b, 1H). (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 292.18.

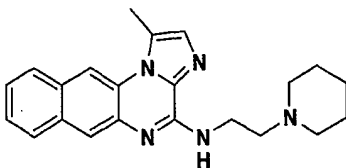
Example 7

1-Methyl-4-(2-hydroxyethylamino)benzo[g]imidazo[1,2-a]quinoxaline



To a solution of 4-chloro-1-methylbenzo[g]imidazo[1,2-a]quinoxaline (0.060 g, 0.225 mmol) (Preparation 4) in 2 mL of THF was added 2-aminoethanol (0.11 mL, 1.80 mmol). The reaction tube was sealed and the mixture stirred at 80°C for 16 hours. The resulting cooled mixture was then taken up in EtOAc, washed with water and brine, dried (Na_2SO_4) and evaporated. The resulting residue was recrystallized using i-PrOH to give Example 7 (0.062 g, 94%); mp $186-188^\circ\text{C}$; IR (KBr, cm^{-1}) 3370, 3147, 1549, 1485, 1414; ^1H NMR (DMSO- d_6) 8.64 (s, 1H), 8.10-8.09 (m, 2H), 7.96 (d, $J = 7.5$, 1H), 7.51-7.46 (m, 3H), 7.37 (s, 1H), 4.91 (t, $J = 5.2$, 1H), 3.70-3.66 (m, 4H), 3.00 (s, 3H); MS (^+ESI , $\text{M} + \text{H}^+$) m/z 293; HPLC: 98.8% (230 nm).

Example 8

1-Methyl-4-(2-piperidin-1-yl-ethylamino)benzo[g]imidazo[1,2-a]quinoxaline

5

To a solution of 4-chloro-1-methylbenzo[g]imidazo[1,2-a]quinoxaline (0.055 g, 0.206 mmol) (Preparation 4) in 5 mL of THF was added 1-(2-aminoethyl)piperidine (0.24 mL, 1.65 mmol). The reaction tube was sealed and the mixture stirred at 80°C for 17 hours. The resulting cooled mixture was then taken up in EtOAc, washed with water and brine, dried (Na₂SO₄) and evaporated. The resulting residue was recrystallized using i-PrOH to give Example 8 (0.063 g, 84%); mp 170-172 °C; IR (KBr, cm⁻¹) 3300, 2932, 1557, 1483, 1408; ¹H NMR (DMSO-d₆) 8.61 (s, 1H), 8.07-8.06 (m, 2H), 7.94 (d, J = 7.6, 1H), 7.49-7.34 (m, 4H), 3.66 (br q, J = 6.5, 2H), 2.97 (s, 3H), 2.59 (br t, J = 6.5, 2H), 2.44 (br s, 4H), 1.54-1.39 (m, 6H); MS (⁺ESI, M + H⁺) m/z 360; HPLC: 97.6% (230 nm).

15

It should be understood that one skilled in the field may make various modifications to the compounds, compositions and schemes described above, applying the ordinary level of skill in the field, without departing from the spirit or scope of the invention. All such modifications are intended to be included within the invention as defined in the appended claims.

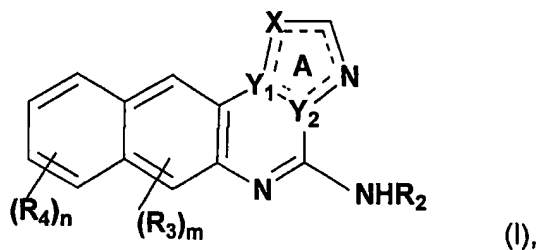
20

CLAIMS

We claim:

1. A compound of the formula:

5



or a pharmaceutically-acceptable salt thereof, wherein

X is NR₁, CR₁, or S;

- 10 Y₁ and Y₂ are nitrogen or carbon, provided that

a) when X is CR₁, at least one of Y₁ and Y₂ is nitrogen, and b) when one of Y₁ and Y₂ is carbon, the other of Y₁ and Y₂ is nitrogen and/or X is NR₁ or S, so that ring A defines a five-membered heteroaryl ring having at least two heteroatoms;

- 15 R₁ is hydrogen, halogen, alkyl, substituted alkyl, cyano, OR₅, NR₅R₆, C(=O)R₅, CO₂R₅, or aryl;

R₂ is alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclo, cycloalkyl, or substituted cycloalkyl;

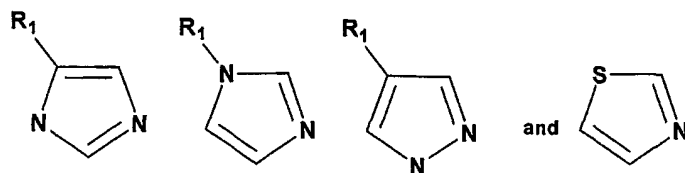
- 20 R₃ and R₄ are independently selected from halogen, alkyl, substituted alkyl, nitro, cyano, OR₇, NR₇R₈, C(=O)R₇, CO₂R₇, SR₇, C(=O)NR₇R₈, NR₇C(=O)R₈, NR₇C(=O)OR₈, S(O)_qR₇, NR₇SO₂R₈, and SO₂NR₇R₈;

R_5 , R_6 , R_7 , and R_8 are independently selected from hydrogen, alkyl, substituted alkyl, and phenyl, or when attached to the same nitrogen atom (as in NR_5R_6 or NR_7R_8) may join together to form a heterocycle or heteroaryl; and

m , n and q are independently 0, 1, or 2.

5

2. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, in which X , Y_1 and Y_2 are selected so that ring A defines one of:



10

3. The compound of claim 1 or a pharmaceutically-acceptable salt thereof, in which:

R_2 is C_{1-4} alkyl optionally substituted with OR_9 or $NR_{10}R_{11}$;

R_9 is hydrogen or lower alkyl; and

15 R_{10} and R_{11} are (i) independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} substituted alkyl, and $-(C=O)C_{1-2}$ alkyl, or alternatively (ii) together form a five to six membered heterocycle or heteroaryl.

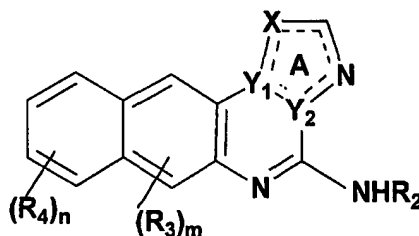
20 4. The compound of claim 1 or a pharmaceutically-acceptable salt thereof, in which

X, Y₁ and Y₂ are selected so that ring A defines one of pyrazolyl, imidazolyl, or thiazolyl;

R₁ is hydrogen, methyl, ethyl, or trifluoromethyl; and

R₂ is C₁₋₂alkyl optionally substituted with one of OH, NH₂, NH(C₁₋₂alkyl),
 5 N(C₁₋₂alkyl)₂, NH(C=O)C₁₋₂alkyl, or a five to six membered heterocycle.

5. A compound having the formula,



10

or a pharmaceutically-acceptable salt thereof, wherein

X is NR₁, CR₁, or S;

Y₁ and Y₂ are nitrogen or carbon, provided that:

a) when X is CR₁, at least one of Y₁ and Y₂ is nitrogen, and b) when one of
 15 Y₁ and Y₂ is carbon, the other of Y₁ and Y₂ is nitrogen and/or X is NR₁ or S,
 so that ring A defines a five-membered heteroaryl ring having at least two
 heteroatoms;

R₁ is hydrogen, halogen, lower alkyl, or trifluoromethyl;

R₂ is C₁₋₄ alkyl optionally substituted with a group selected from hydroxy,
 20 alkoxy, NH₂, NH(alkyl), N(alkyl)₂, NH(substituted alkyl), N(substituted alkyl)₂, and
 NH(C=O)alkyl, and heterocycle;

R_3 and R_4 are independently halogen, lower alkyl, substituted lower alkyl, nitro, cyano, alkoxy, amino, $-CO_2H$, $-C(=O)H$, or alkylthio; and

m and n are independently 0, 1, or 2.

- 5 6. The compound of claim 5, or a pharmaceutically-acceptable salt thereof, in which:

R_2 is C_{1-2} alkyl optionally substituted with a group selected from OH , NH_2 , $NH(C_{1-2}alkyl)$, $N(C_{1-2}alkyl)_2$, $NH(C_{1-2}substituted\ alkyl)$, $N(C_{1-2}substituted\ alkyl)_2$, and piperidinyl.

10

7. The compound of claim 1, selected from (i)

benzo[g]-4-(2-N-methylaminoethylamino)-1-methylimidazo[1,2-a]quinoxaline;

benzo[g]-4-methylamino-1-methylimidazo[1,2-a]quinoxaline;

benzo[g]-4-(2-N-methylaminoethylamino)-1-methylpyrazolo[1,2-a]quinazoline;

- 15 benzo[g]-4-methylamino-1-methylpyrazolo[1,2-a]quinoxaline;

1-methyl-4-methylaminobenzo(g)-imidazo(4,5-c)quinoline;

1-methyl-4-(2-N-methylaminoethylamino)benzo(g)imidazo(4,5-c)quinoline,

1-methyl-4-methylaminobenzo(g)-thiazolo(4,5-c)quinoline;

1-methyl-4-(2-N-methylaminoethylamino)benzo(g)thiazolo(4,5-c)quinoline;

- 20 1-Methyl-4-(2-hydroxyethylamino)benzo[g]imidazo[1,2-a]quinoxaline,

1-Methyl-4-(2-piperidin-1-yl-ethylamino)benzo[g]imidazo[1,2-a]quinoxaline; and

(ii) a pharmaceutically-acceptable salt thereof.

8. A pharmaceutical composition comprising (a) at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

5 9. Use of a compound according to claim 1 comprising administering to a mammal in need of treatment a therapeutically-effective amount of at least one compound according to claim 1.

10 10. Use of a compound according to claim 9 comprising treating said mammal for an inflammatory or immune disease selected from rheumatoid arthritis, asthma, inflammatory bowel disease, chronic obstructive pulmonary disease, and psoriasis.

15 11. Use of a compound according to claim 9 comprising treating said mammal for HIV, HSV-1, breast cancer, prostate cancer, or Hodgkin's lymphoma.

THIS PAGE BLANK (USPTO)